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10/505,475	08/24/2004	Guido Mayer	3165-105	1724

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EXAMINER

OH, TAYLOR V

ART UNIT	PAPER NUMBER
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1625

DATE MAILED: 11/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/505,475

Applicant(s)

MAYER ET AL.

Examiner

Taylor Victor Oh

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 August 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 6-31 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 6-31 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>8/24/04</u> . | 6) <input type="checkbox"/> Other: _____ |

The Status of Claims:

Claims 6-31 are pending.

Claims 6-31 have been rejected.

DETAILED ACTION

1. Claims 6-31 are under consideration in this Office Action.

Priority

2. It is noted that this application is a 371 of PCT/EP03/01160 (02/06/2003).

Drawings

3. None.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for iron, indium and halides, oxides and triflates thereof as a catalyst, does not reasonably provide enablement for any catalysts generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly

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connected, to include all kinds of catalysts unrelated to the claimed invention commensurate in scope with these claims.

Furthermore, the instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without **undue experimentation**.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation, citing *Ex Parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

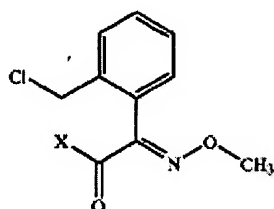
- 1) the quantity of experimentation necessary,
- 2) the amount of direction or guidance provided,
- 3) the presence or absence of working examples,
- 4) the nature of the invention,
- 5) the state of the prior art,
- 6) the relative skill of those in the art,
- 7) the predictability of the art, and
- 8) the breadth of the claims.

The Nature of the Invention

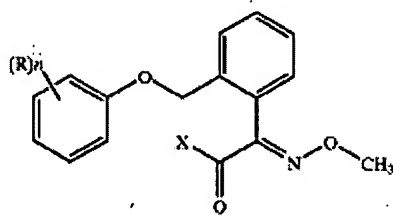
The nature of the invention is

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6. A process for preparing a 2-(chloromethyl) phenylacetic acid derivative of formula I,



where X is C1-C4-alkoxy or methylamino,
said process comprising
either cleaving a compound of formula II,



where R is C1-C4-alkyl, C1-C4-alkoxy, C1-C2-haloalkyl, C1-C4-alkylcarbonyl, C1-C4-alkylcarbonyloxy, halogen, nitro or cyano and X is as defined above, with hydrogen chloride, in the presence of an inert solvent and a catalyst.

The State of the Prior Art

The states of the prior art are described as followed:

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[0004] J. Chem. Research (S) 232-3 (1985) and J. Org. Chem. 64, 4545 (1981) disclose methods for cleaving benzyl ethers in the presence of specific Lewis acids such as sodium iodide/boron trifluoride or iron(III) chloride on silica. The Lewis acids are used in greater than stoichiometric quantities, which makes the process uneconomical.

[0005] Synlett (10), 1575-6 (1999) describes a process for cleaving 4-nitrobenzyl ethers in the presence of indium and aqueous ammonium chloride. Indium is used in an excess of more than 8 equivalents based on the ether to be cleaved.

[0006] A process for preparing 2-(chloromethyl)phenyl acetic acid derivatives of the formula I by cleaving the appropriate benzyl ethers II is described in WO-A 97/21686. This involves admixing the benzyl ether II with an excess of two or more mol equivalents of boron trichloride.

As the prior art have been discussed in the above, there is no conclusive data that all kinds of catalysts would work to produce the final desired product except some catalysts, such as, Lewis acids and Indium.

The predictability or lack thereof in the art

In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that any catalyst would not work on the claimed process in the same way as those catalysts such as carbonates, alkali bicarbonates, alkalis, and mixtures thereof disclosed in the specification. For example, Gardener (US 3,878,261) discloses the super acid catalyst of SbF_5 and $\text{CF}_3\text{SO}_3\text{H}$ used for isomerizing paraffins containing 4 to 12 carbons in a feed stream (see abstract page); furthermore, according to the text book, March's Advanced Organic Chemistry (March et al, 4th ed. 1992), it describes that another super acid, FSO_3H -

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SbF₆, is used in the formation of a carbocation, such as tert-butyl cation (see p. 219, the fourth paragraph) from isobutane unlike the claimed process.

Furthermore, the specification of the claimed invention does support the very idea of the unpredictable aspect of the catalysts by disclosing those specific and workable catalysts for the decarboxylation in the above, not all kinds of the catalyst known in the art.

Moreover, chemical reactions are well-known to be unpredictable, *In re Marzocchi*, 169 USPQ 367, *In re Fisher*, 166 USPQ 18. Additionally, catalytic processes, such as are present here, are inherently unpredictable. The U.S. District Court District of Connecticut held in *MOBIL OIL CORPORATION v. W.R. GRACE & COMPANY*, 180 USPQ 418 that "there is an inherent mystery surrounding the unpredictability of the performance of catalysts; a mystery which is generally recognized and acknowledged by chemists in the cracking art. This is one more reason why the presumption of patent validity "should not be disregarded especially in a case of this sort where the intricate questions of [bio]chemistry involved are peculiarly within the particular competence of the experts of the Patent Office." *Merck & Co. v. Olin Mathieson Chemical Corp.*, 253 F.2d 156, 164, 116 USPQ 484, 490 (4th Cir. 1958)". "The catalytic action can not be forecast by its chemical composition, for such action is not understood and is not known except by actual test, *Corona Cord Tire Co. v. Dovan Chemical Corp.*, 276 U.S. 358, 368-369 (1928). Also see, *Application of Grant*, 304 F.2d 676, 679, 134 USPQ 248, 250-251 (CCPA 1962); *Rich Products Corp. v. Mitchell Foods, Inc.*, 357 F.2d 176, 181, 148 USPQ 522, 525-526 (2d Cir. 1966), cert. denied 385 U.S. 821, 151 USPQ 757 (1966); *Ling-Temco-Vought, Inc. v. Kollsman Instrument Corp.*, 372 F.2d 263, 268, 152 USPQ 446, 450-451 (2d Cir. 1967);

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Georgia-Pacific Corp. v. United States Plywood Corp., 258 F.2d 124, 132-133, 118 USPQ 122, 128-129."

Therefore, from the above, it is clear that the use of a generic phrase "a catalyst" can not ensure to form the desired claimed product in a good yield.

The amount of direction or guidance present

The direction present in the instant specification is that not any catalyst can be led to the formation of the desired product. According to the specification, it is silent as to how any catalyst can be led to the formation of the desired product and fails to provide guidance as to whether any catalyst is sufficient enough to allow to form the desired product in sufficient quantities; the specification fails to provide a correlation between the claimed process of the invention and the functional language of any catalyst.

The presence or absence of working examples

In the instant case, the claim encompasses all the various catalysts. Applicants' specification provide only four particular exemplified catalyst compounds, such as iron chloride, indium chloride, aluminum chloride, tin tetrachloride as shown in the examples 1-5 for producing the desired compound in the specification. However, these can not be the representatives for all the catalysts which would work for the claimed process. Thus, the specification fails to provide working examples as to how other types of catalysts can be resulted in the claimed products, i.e. again, there is no correlation between the functional language of any catalyst and the desired final product.

The breadth of the claims

The breadth of the claims is that any catalyst would work on the claimed process in the same way as those disclosed catalyst in the specification without considering the affect or impact of the different types of acidic catalysts on the starting compounds; for example, the super acid $\text{FSO}_3\text{H-SbF}_6$ disclosed in March's Advanced Organic Chemistry (March et al, 4th ed. 1992) has a high likelihood of removing hydrogen ions from the reactant, the benzyl ether instead of cleaving the ether bond to form the desired 2-(chloromethyl)phenylacetic acid product, thereby detrimentally affecting the yield of the desired final product.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine which one of the catalysts would be capable of forming the desired product and would furthermore then have to determine which one of the catalysts would not be resulted in the claimed desired compounds in a sufficient quantity.

The level of the skill in the art

Even though the level of skill in the process of cleavage of ether is high, based on the unpredictable nature of the invention and the state of the prior art and the extreme breadth of the claims and lack of guidance and direction for other types catalysts than those disclosed catalysts in the specification, one skilled in the art could not employ the claimed invention without undue experimentation. The quantity of experimentation needed is undue experimentation.

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in

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undue experimentation to test which acidic catalyst can be employed to produce the desired claimed compound encompassed in the instant claims, with no assurance of success.

Claim 26 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for tetraalkylammonium halides and tri alkyl phenyl ammonium halides, and bis-triarylammonium halides as a phase transfer catalyst does not reasonably provide enablement for all phase transfer catalysts. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to include all phase transfer catalysts unrelated to the claimed invention commensurate in scope with these claims.

Furthermore, the instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation, citing *Ex Parte Forman*, 230 USPQ 546 (BdApl 1986) at 547 the court recited eight factors:

- 1) the quantity of experimentation necessary,
- 2) the amount of direction or guidance provided,
- 3) the presence or absence of working examples,
- 4) the nature of the invention,
- 5) the state of the prior art,
- 6) the relative skill of those in the art,
- 7) the predictability of the art, and

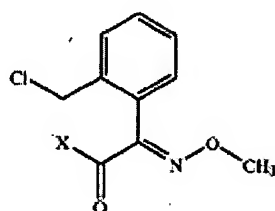
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8) the breath of the claims.

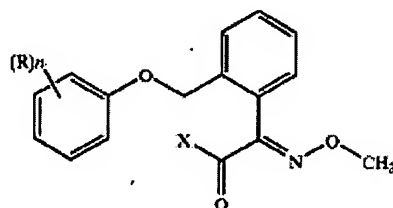
The Nature of the Invention

The nature of the invention is

6. A process for preparing a 2-(chloromethyl) phenylacetic acid derivative of formula I,



where X is C1-C4-alkoxy or methylamino,
said process comprising
ether cleaving a compound of formula II,



where R is C1-C4-alkyl, C1-C4-alkoxy, C1-C2-haloalkyl,
C1-C4-alkylcarbonyl, C1-C4-alkylcarbonyloxy, halo-
gen, nitro or cyano and X is as defined above, with
hydrogen chloride, in the presence of an inert solvent
and a catalyst.

,further ether cleaving reaction in

a biphasic system in the presence of a phase transfer catalyst.

The State of the Prior Art

The states of the prior art are described as followed:

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[0004] J. Chem. Research (S) 232-3 (1985) and J. Org. Chem. 64, 4545 (1981) disclose methods for cleaving benzyl ethers in the presence of specific Lewis acids such as sodium iodide/boron trifluoride or iron(III) chloride on silica. The Lewis acids are used in greater than stoichiometric quantities, which makes the process uneconomical.

[0005] Synlett (10), 1575-6 (1999) describes a process for cleaving 4-nitrobenzyl ethers in the presence of indium and aqueous ammonium chloride. Indium is used in an excess of more than 8 equivalents based on the ether to be cleaved.

[0006] A process for preparing 2-(chloromethyl)phenyl acetic acid derivatives of the formula I by cleaving the appropriate benzyl ethers II is described in WO-A 97/21686. This involves admixing the benzyl ether II with an excess of two or more mol equivalents of boron trichloride.

As the prior art have been discussed in the above, there is no conclusive data that all the different types of phase transfer catalysts would be required to produce the final desired product.

The predictability or lack thereof in the art

In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that any phase transfer catalyst would not work on the claimed process in the same way as those disclosed phase transfer catalysts, tetraalkylammonium halides and tri alkyl phenyl ammonium halides, and bis-triarylammonium halides, in the specification. For example, the text book of Mark's Advanced Organic Chemistry does emphasize that not all quaternary salts and cryptands work equally well in all situations and

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some experimentation is often required to find the optimum catalyst the examiner (see page 456, lines 19-20).

Moreover, chemical reactions are well-known to be unpredictable, *In re Marzocchi*, 169 USPQ 367, *In re Fisher*, 166 USPQ 18. Additionally, catalytic processes, such as are present here, are inherently unpredictable. The U.S. District Court District of Connecticut held in *MOBIL OIL CORPORATION v. W.R. GRACE & COMPANY*, 180 USPQ 418 that "there is an inherent mystery surrounding the unpredictability of the performance of catalysts; a mystery which is generally recognized and acknowledged by chemists in the cracking art. This is one more reason why the presumption of patent validity "should not be disregarded especially in a case of this sort where the intricate questions of [bio]chemistry involved are peculiarly within the particular competence of the experts of the Patent Office." *Merck & Co. v. Olin Mathieson Chemical Corp.*, 253 F.2d 156, 164, 116 USPQ 484, 490 (4th Cir. 1958)". "The catalytic action can not be forecast by its chemical composition, for such action is not understood and is not known except by actual test, *Corona Cord Tire Co. v. Dovan Chemical Corp.*, 276 U.S. 358, 368-369 (1928). Also see, *Application of Grant*, 304 F.2d 676, 679, 134 USPQ 248, 250-251 (CCPA 1962); *Rich Products Corp. v. Mitchell Foods, Inc.*, 357 F.2d 176, 181, 148 USPQ 522, 525-526 (2d Cir. 1966), cert. denied 385 U.S. 821, 151 USPQ 757 (1966); *Ling-Temco-Vought, Inc. v. Kollsman Instrument Corp.*, 372 F.2d 263, 268, 152 USPQ 446, 450-451 (2d Cir. 1967); *Georgia-Pacific Corp. v. United States Plywood Corp.*, 258 F.2d 124, 132-133, 118 USPQ 122, 128-129."

Therefore, the use of a generic phrase "a phrase transfer catalyst" can not ensure to form the desired claimed product in a good yield.

The amount of direction or guidance present

The direction present in the instant specification is that not any phrase transfer catalyst can be led to the formation of the desired product.

According to the specification, it is silent as to how any phrase transfer catalyst can be led to the formation of the desired product and fails to provide guidance as to whether any phrase transfer catalyst is sufficient enough to allow to form the desired product in sufficient quantities; the specification fails to provide a correlation between the claimed process of the invention and the functional language of any phrase transfer catalyst.

The presence or absence of working examples

There is no working examples using the phrase transfer catalyst for producing the desired compound in the specification. From this, it follows that there is no evidence that all the phrase transfer catalysts would work for the claimed process. Thus, the specification fails to provide working examples as to how the other types of phrase transfer catalysts can be resulted in the claimed products, i.e. again, there is no correlation between the functional language of any phrase transfer catalyst and the desired final product.

The breadth of the claims

The breadth of the claims is that any phrase transfer catalyst would work on the claimed process in the same way as those disclosed phrase transfer catalyst without considering the affect or impact of the different phrase transfer catalysts on the starting compound, thereby affecting the yield of the desired final product.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine which one of the phrase transfer catalysts would be capable of forming the desired product and would furthermore then have to determine which one of the phrase transfer catalysts would not be resulted in the claimed desired compounds in a sufficient quantity.

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which phrase transfer catalyst can be employed to produce the desired claimed compound encompassed in the instant claims, with no assurance of success.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 6, the term " ether cleaving a compound of formula II " is recited. The expression is vague and indefinite because the phrase " ether cleaving a compound of formula II " would mean that the ether cleaving compound was the compound of formula II ; there is

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uncertainty as to which compound is for ether cleaving compound and which compound is for the reactant for the process. Therefore, an appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

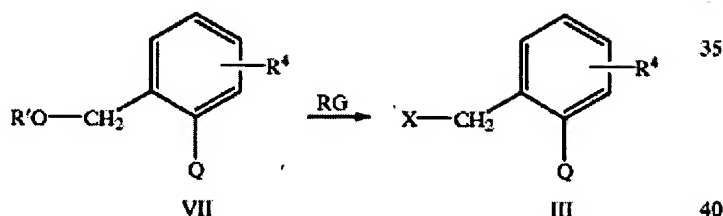
A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 6-7, 17-18, 21, and 28-31 are rejected under 35 U.S.C. 102(b) as being anticipated clearly by Oberdorf et al (US 6,114,342).

Oberdorf et al discloses the followings (see col. 5, lines 32-60):

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R'=unsubstituted or substituted alkyl or unsubstituted or substituted aryl

No.	RG	X
III.1	BCl ₃	Cl
III.2	HBr	Br

by means of cleavage with, for example, boron trichloride (for III.1) or hydrogen bromide (for III.2) in inert solvents such as halogenated hydrocarbons at from (-30) to 40° C. An advantageous synthesis from the corresponding compound VII where R'=2-tolyl (see EP-A 477 631, Table 1, No. 94) is described in Examples 1 to 3.

The preparation of the compounds III where Q is C(=NOCH₃)-COOCH₃ has been disclosed in EP-A 363 818.

The compounds VII can also be employed in the form of their salts, in particular as the hydrohalides (eg. hydrochloride or hydrobromide). If salts are used, it is expedient to carry out the reaction in the presence of a base (eg. alkaline earth metal or alkali metal alkoxides, or alkaline earth metal or alkali metal hydroxides, eg. sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium hydroxide, potassium hydroxide and calcium hydroxide).

(see col. 3 ,lines 60-67).

This is identical with the claims.

Claim Rejections - 35 USC § 103

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

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claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

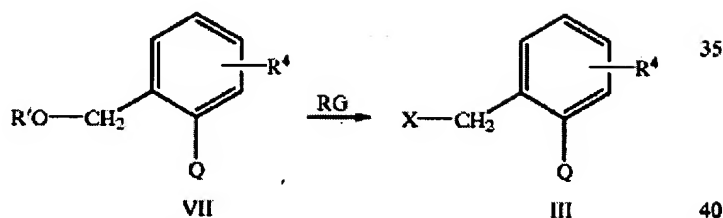
The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 6-9, 11-25, and 27-31 are rejected under 35 U.S.C. 102(b) as being anticipated clearly by Oberdorf et al (US 6,114,342) in view of Jemty et al (J. Org. Chem. 1981, 46, 4545-4551) and Vankar et al (J. Chem. Research (S), 1985, 232-233).

Oberdorf et al discloses the followings (see col. 5, lines 32-60):

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R'=unsubstituted or substituted alkyl or unsubstituted or substituted aryl

No.	RG	X
III.1	BCl ₃	Cl
III.2	HBr	Br

by means of cleavage with, for example, boron trichloride (for III.1) or hydrogen bromide (for III.2) in inert solvents such as halogenated hydrocarbons at from (-30) to 40° C. An advantageous synthesis from the corresponding compound VII where R'=2-tolyl (see EP-A 477 631, Table 1, No. 94) is described in Examples 1 to 3.

The preparation of the compounds III where Q is C(=NOCH₃)-COOCH₃ has been disclosed in EP-A 363 818.

The compounds VII can also be employed in the form of their salts, in particular as the hydrohalides (eg. hydrochloride or hydrobromide). If salts are used, it is expedient to carry out the reaction in the presence of a base (eg. alkaline earth metal or alkali metal alkoxides, or alkaline earth metal or alkali metal hydroxides, eg. sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium hydroxide, potassium hydroxide and calcium hydroxide).

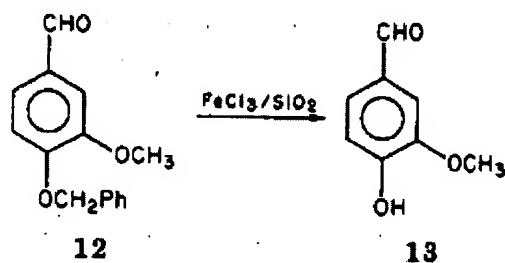
However, the instant invention differs from the prior art in that the concentration of the catalyst, such as hydrogen chloride is unspecified ; the use of Lewis base is also unspecified. .

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Jemphy et al (J. Org. Chem. 1981, 46. 4545-4551) discloses the benzyl ether cleavage using $\text{FeCl}_3/\text{SiO}_2$ in the followings (see page 4548, left col.):

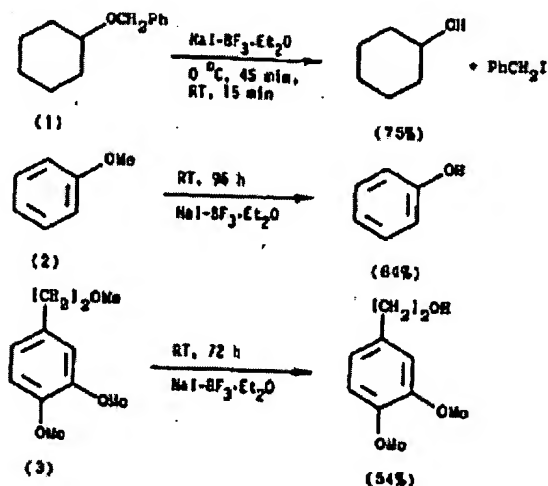
Cleavage of Benzyl Ethers. As part of this study of phenol ether oxidations we attempted to oxidize *O*-benzylpseudocodamine (3c) with $\text{FeCl}_3/\text{SiO}_2$. The sole product was isolated and identified as the debenzylated (\pm)-pseudocodamine 3d in 40% yield. All further attempts to generate any oxidation products failed. In fact, by increasing the amount of reagent to 5 molar equiv and leaving the reaction mixture of $\approx 80^\circ\text{C}$ on the rotary evaporator overnight, a new product was isolated which contained at least four chlorine atoms as determined by mass spectral analysis.

In an attempt to determine the scope and limitations of $\text{FeCl}_3/\text{SiO}_2$ for the cleavage of benzyl ethers, a number of simple benzyl ethers were treated with this reagent. The procedure was the same as for oxidations except that the phenol products were isolated by aqueous base extraction, subsequent acidification of the aqueous phase, and back-extraction with a volatile organic solvent. Pure phenols were always obtained in this manner, often in high yield (Table III). It was shown, for example, that compounds 12 and 14 gave excellent yields of vanillin (13) and isovanillin (15), using 1.1 equiv of FeCl_3 at 30°C for 1 h. Dichromate titration showed that no Fe(II) was generated. These are not oxidative cleavages.¹⁷ Use of 0.5 equiv of reagent gave a 43% yield of 13 and 12, indicating that the FeCl_3 is reacting stoichiometrically.



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Furthermore, Vankar et al discloses the selective cleavage of benzyl ethers using the boron trifluoride-ether and sodium iodide reagent system as shown below (see page 232, both cols):



Fujita *et al.*⁴ and Kiso *et al.*⁵ have reported the use of boron trifluoride-ether-ethanethiol or dimethyl sulphide and trifluoroacetic acid-thioanisole systems, respectively, for the deprotection of methyl and benzyl ethers.

(see page 232, right col.

Table Cleavage of benzyl ethers

Entry	Benzyl ether	BF ₃ ·Et ₂ O (mmol)	NaI (mmol)	Conditions ^a	Yield (%) ^b
1	(PhCH ₂) ₂ O	1	2.4	0 °C for 1 h, then RT for 30 min	90 ^{c,d}
2	3-Naphthyl-OCH ₂ Ph	1.4	1.4	0 °C for 1 h, then RT for 2 h	90
3	cyclo-C ₆ H ₁₁ -OCH ₂ Ph	1.25	1.25	0 °C for 45 min, then RT for 15 min	75
4	1-PhCH ₂ O-2-Me-cyclo-C ₆ H ₁₀	1.25	1.25	0 °C for 45 min, then RT for 15 min	85
5	1-PhCH ₂ O-4-Ph-cyclo-C ₆ H ₁₀	1.25	1.25	0 °C for 30 min, then RT for 15 min	94
6	1,2-(MeO) ₂ -4-(PhCH ₂ O[CH ₂) ₂ -C ₆ H ₃	1.25	1.25	0 °C for 1 h, then RT for 1.5 h	90
7	PhS[CH ₂) ₃ OCH ₂ Ph	2	2	0 °C for 1 h, then RT for 7 h	80
8	3-MeOCH ₂ -C ₆ H ₄ O[CH ₂) ₂ OMe	2	2	0 °C for 2 h	94 ^c
9	4-MeO-C ₆ H ₄ CH ₂ OMe	1.4	1.4	0 °C for 2 h	94 ^c
10	PhOCH ₂ Ph	1.4	1.4	0 °C for 5 h, then RT for 16 h	85

^aRT = Room temperature.^bExcept for entries labelled c, benzyl iodide was also isolated in ca. 80% yield.^cIsolated as the iodide.^dYield is based on one benzyl group.

(see page 233, table).

With respect to the use of hydrogen chloride in the claimed process, the Oberdorf et al prior art does teach the employment of the hydrogen bromide ; both are commonly involved in using the halogen base in their respective acidic forms; there is a teaching of equivalence among them in their usage in the absence of an unexpected result. Therefore, it would have been obvious to the skilled artisan in the art to be motivated to use the well-known hydrogen chloride as an alternative to the hydrogen bromide into the Oberdorf 'et al process. This is because the skilled artisan in the art would expect such a combination to be successful as the guidance shown in the e Oberdorf 'et al .


Oberdorf et al does disclose the process of preparing 2-(chloromethyl)phenyl acetic acid derivatives by cleaving the corresponding benzyl ether the followings in the presence of hydrogen bromide; similarly, Jempty et al expresses the benzyl ether cleavage using $\text{FeCl}_3/\text{SiO}_2$; furthermore, Vankar et al clearly discloses the selective cleavage of benzyl ethers using the boron trifluoride-ether and Lewis base, ethanethiol, reagent system. All the prior art are commonly involved in the cleavage of the benzyl ether compound. Therefore, it would have been obvious to the skilled artisan in the art to be motivated to incorporate the Jempty's et al iron and Vankar's et al Lewis base into the Oberdorf et al process in order to speed up the reaction process and react all the reactants to its completion. This is because the skilled artisan in the art would expect such a combination to be successful , efficient ,and less costly.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taylor Victor Oh whose telephone number is 571-272-0689. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thomas McKenzie can be reached on 571-272-0670. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Primary Examiner
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11/11/06